To combine or not to combine: anti-vascular endothelial growth factor therapies in EGFR mutation positive non-small cell lung cancer

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The concomitant use of vascular endothelial growth factor (VEGF) inhibitors with cytotoxic chemotherapy reportedly enhances treatment efficacy in patients with non-small cell lung cancer (NSCLC). The anti-angiogenic monoclonal antibody bevacizumab targets the VEGF signaling pathway and has been shown to provide additional efficacy when used in combination with first-line platinum-based chemotherapy in several trials for non-squamous NSCLC (1-3). The combination of docetaxel and ramucirumab, an anti-VEGFR2 antibody, has been established as a standard treatment in patients with refractory NSCLC who experienced progression after a first-line platinum-based combination (4).

In addition to cytotoxic agents, the combination of erlotinib and bevacizumab has the potential to prolong progression-free survival (PFS) in unselected populations of patients with NSCLC (5,6). In a subgroup analysis of EGFR-mutation-positive participants in the phase 3 BeTa study examining second-line treatments for NSCLC (12 patients treated with erlotinib and bevacizumab and 18 with erlotinib alone), the median PFS period for patients with EGFR-mutation-positive disease who were treated with erlotinib plus bevacizumab was substantially higher than that in patients treated with erlotinib alone (17.1 *vs.* 9.7 months) (5).

About 10 years ago, first-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib and erlotinib were shown, for the first time, to exert an efficacy that was superior to that of cytotoxic anticancer agents in patients with NSCLC harboring an EGFR mutation.

When PFS was examined in the LUX-Lung7 trial, the second-generation EGFR-TKI afatinib was shown to have a hazard ratio of 0.74 (95% CI, 0.57–0.95), compared with gefitinib (7). However, the median PFS periods were 11.0 and 10.9 months, respectively. In 2018, the ARCHER1050 trial reported the results of a comparison between dacomitinib, another second-generation EGFR-TKI, and gefitinib (8). In this study, dacomitinib was more effective than gefitinib in terms of both PFS (HR, 0.59; 95% CI, 0.47–0.74) and overall survival (OS) (HR, 0.76; 95% CI, 0.58–0.99).

Osimertinib, a third-generation EGFR-TKI, is an effective drug against the T790M mutation, which is the main resistance mechanism. The FLAURA trial was the first phase III trial comparing osimertinib and first-generation EGFR-TKIs (gefitinib, erlotinib) in patients with NSCLC without previous treatment (9). Patients assigned to first-generation EGFR-TKIs were also offered osimertinib as a crossover treatment after disease progression. Osimertinib showed better results than the first-generation EGFR-TKIs in terms of both PFS (HR, 0.46; 95% CI, 0.37–0.57) and OS (HR, 0.799; 95% CI, 0.641–0.997).

On the other hand, attempts to use an EGFR-TKI and an angiogenesis inhibitor in combination have been made

Table 1 Pivotal trials for EGFR (+) NSCLC

Trial	FLAURA	ARCHER	LUX-Lung7	RELAY	JO25567	NEJ026
Phase	III	III	II	III	II	III
Primary endpoint	PFS	PFS	PFS, TTF, OS	PFS	PFS	PFS
Number of patients	279/277	227/225	160/159	224/225	77/77	112/112
Arm (experimental/control)	Osimertinib/gefitinib or erlotinib	Dacomitinib/gefitinib	Afatinib/gefitinib	Ramucirumab, erlotinib /erlotinib	Bevacizumab, erlotinib /erlotinib	Bevacizumab, erlotinib /erlotinib
Brain metastases	Included	Excluded	Included	Excluded	Excluded	Included
ORR (%)	–	–	73/56	76/75	69/63	72.3/66.1
PFS (months)	18.9/10.2	14.7/9.2	11/10.9	19.4/12.4	16.4/9.8	16.9/13.3
PFS, HR (95% CI)	0.46 (0.37–0.57)	0.59 (0.47–0.74)	0.74 (0.57–0.95)	0.591 (0.461–0.760)	0.52 (0.35–0.76)	0.605 (0.417–0.877)
PFS (ex19 del, months)	21.4/11	16.5/9.2	14.7/12.9	19.6/12.5	18/10.3	16.6/12.4
PFS (L858R, months)	14.4/9.5	12.3/9.8	12.9/9.8	19.4/11.2	13.9/7.1	17.4/13.7
OS (months)	38.6/31.8	34.1/26.8	27.9/24.5	–	47/47.4	–
OS, HR (95% CI)	0.799 (0.641–0.997)	0.76 (0.58–0.99)	0.86 (0.66–1.12)	–	0.81 (0.53–1.23)	–
%AE ≥ grade 3	18/29	–/–	31.3/19.5	72/54	91/53	56.3/37.7

NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; AE, adverse events; ORR, objective response rate.

for the treatment of patients with EGFR-mutation-positive NSCLC. The JO25567 trial was a randomized phase II trial comparing erlotinib with erlotinib + bevacizumab (10). The median PFS period for erlotinib was 9.8 months, compared with 16.4 months in the combination group (HR, 0.52; 95% CI, 0.35–0.76), showing the significant efficacy of using a combination of erlotinib and bevacizumab. The NEJ026 trial was the first phase III trial using EGFR-TKIs and angiogenesis inhibitors (11). As described above, the bevacizumab combination group had a statistically significant longer PFS period, with an HR of 0.605 (95% CI, 0.417–0.877). In addition, the results of the RELAY study, a phase three study using ramucirumab (another angiogenesis inhibitor), have also been reported (12). In this study, the PFS was clearly prolonged, with an HR of 0.591 (95% CI, 0.461–0.760) in the combined treatment group that included the angiogenesis inhibitor. In the NEJ026 and RELAY studies, OS analyses were planned but have not yet been reported.

In summary, osimertinib, dacomitinib, erlotinib + bevacizumab, and erlotinib + ramucirumab all showed significant results in terms of PFS, which was the primary endpoint of the studies. Among them, the efficacies of osimertinib and dacomitinib have also been confirmed in terms of OS (*Table 1*).

An improvement in drug delivery is one possible mechanism explaining the synergistic efficacy provided by anti-VEGF inhibitors. Several studies have reported that bevacizumab changes the tumor vessel physiology, resulting in an increased intra-tumoral concentration of drugs (13,14). Concerning the resistance mechanism of EGFR-TKIs in patients with EGFR-mutated NSCLC, one study suggested that patients on lower doses of EGFR-TKIs tend to develop treatment resistance earlier than those who receive higher doses (15). When EGFR-TKIs are used in combination with anti-VEGF inhibitors, the higher intra-tumoral concentration of EGFR-TKIs could delay the appearance of resistant cells. In addition to the increased concentration provided by improved drug delivery, VEGF inhibition might be effective in tumors harboring resistance mutations that act against EGFR-TKIs. In preclinical studies, blocking the VEGF signaling pathway enabled the T790M resistance mutation to be overcome (16,17).

There are some obvious drawbacks to combining anti-VEGF and EGFR-TKIs. This combination cannot be used in patients with contraindications to anti-VEGF, such as macrovascular invasion or a history of hemoptysis. Furthermore, the need for a 3-week infusion schedule for bevacizumab and a 2-week infusion schedule for ramucirumab is inconvenient for the patients. Finally, anti-VEGF and EGFR-TKI combination therapy clearly increases the risk of

adverse events, compared with osimertinib.

The combined use of anti-VEGF and EGFR-TKIs has shown results that exceed those of dacomitinib and afatinib in terms of PFS, and the median PFS was comparable to that achievable using osimertinib. Unfortunately, patients with T790M resistance mutations cannot be identified prior to their first treatment; however, if anti-VEGF and EGFR-TKIs are used in the initial treatment and T790M mutations are subsequently identified, osimertinib can be used and a very long OS can be expected. In a subset analysis, EGFR-TKI monotherapy, including osimertinib, tended to result in a poor PFS in patients with L858R mutation-positive disease; however, anti-VEGF and EGFR-TKI combination therapy was shown to be effective regardless of the mutation type (*Table 1*). In addition, patients with brain metastases and pleural effusion were also registered in the NEJ026 study, and a favorable PFS was shown in the anti-VEGF combination group in these subsets (11). These findings suggest that combination therapy with anti-VEGF and EGFR-TKI confers important advantages, and the next step will be to examine the effects of combination therapy with bevacizumab or ramucirumab and osimertinib [TORG1833 (JapicCTI-184146), UMIN000030142, NCT03909334, WJOG9717L (UMIN000030206)].

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Footnote

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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